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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,558	01/19/2000	Robert Busby	109272.130	3300

7590 03/06/2002
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EXAMINER

DAVIS, KATHARINE F

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 03/06/2002

23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/487,558

Applicant(s)

BUSBY ET AL.

Examiner

Katharine F. Davis

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 February 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-28, 102 and 103 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-28, 102 and 103 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10 & 16
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

This Office Action is in response to the Response filed on November 21, 2001, the Supplemental Response filed on January 18, 2002, the Second Supplemental Response filed on February 13, 2002 and the Sequence Letters filed on February 13 and 20, 2002. Claims 1-28, 102 and 103 are pending in the instant application.

A reference to prior application 60/160,587 has been inserted into the first sentence of the instant specification. The objection to the specification has been withdrawn in view of the entry of the corrected Sequence Listing filed on February 20, 2002. The objections to claims 102 and 103 have been withdrawn in view of the amendments to the claims.

Specification

The amendment to the specification filed on February 13, 2002 has not been entered because it does not comply with 37 C.F.R. 1.121. It is required that the amended paragraph(s) of the specification be re-written to indicate the changes made by the amendment(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28, 102 and 103 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

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application was filed, had possession of the claimed invention. This rejection is maintained for the reasons made of record in the Office Action mailed on May 22, 2001. Applicants' arguments presented on pages 3-5 of the Response filed November 21, 2001 and on pages 2-3 of the Supplemental Response filed on January 18, 2002 have been carefully considered but have not been found to be persuasive. Applicants' representative emphasizes (pages 2-3 of the Supplemental Response filed on January 18, 2002) the claimed invention relates to methods for improving secondary metabolite expression in production fungi utilizing particular classes of regulatory genes. Such genes may be known or novel; thus the claimed invention is not a "DNA invention." The examiner agrees that the claimed invention is not a "DNA invention"; however Applicants' admit by the above assertion that the claimed invention encompasses genetic manipulation of any metabolic pathway resulting in an overproduction of any secondary metabolite in any type of fungi. In order to practice this claimed invention one must possess knowledge of the regulation of these pathways and the genes involved in the regulation and further to know the pathways and genes as applicable in many types of fungi. The possession (description) of this knowledge is what the written description rejection is based on, not the possession (description) of the genes disclosed in the instant specification as is required in a "DNA invention".

Applicants state that the specification does describe and identify how to modulate genes in fungal strains in addition to those actually demonstrated in the Examples but do not reference specific page numbers in the specification. Although the specification describes how to identify fungal homologs of regulatory genes, function of the homologs cannot be assumed nor can the homologs be assumed to operate interchangeably in any fungal strain. Applicants' refer to the

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specific genes listed on page 9 of the instant specification and point out that these genes can be used to modulate the expression of a gene involved in regulation of a secondary metabolite by overexpression of the gene. However, which gene (or genes) is experiencing modulated expression because of the overexpression of one of the genes listed on page 9? What metabolic pathways are affected by the overexpression? The instant specification is silent with regard to these questions. Furthermore, although the specification describes what is meant by certain regulators/modulations (for example; conditional gene expression, identification of dominant mutations, peptide modulators) it does not describe what metabolic pathways and genes are affected by these regulators/modulations.

It is determined that Applicants' arguments are insufficient to overcome the rejection. Thus, for both the reasons above and the reasons made of record in the previous Office Action mailed on May 22, 2001, the rejection of claims 1-28, 102 and 103 under 35 U.S.C. 112, first paragraph is maintained.

Claims 1-28, 102 and 103 remain rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for the four examples (described in the previous Office Action mailed on May 22, 2001), does not reasonably provide enablement for methods of modulation of any gene in any fungus to improve the production of any secondary metabolite. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is maintained for the reasons made of record in the previous Office Action

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mailed on May 22, 2001. Applicants' arguments presented on pages 5-6 of the Response filed November 21, 2001 and on pages 1-2 of the Supplemental Response filed on January 18, 2002 have been carefully considered but have not been found to be persuasive. The declaration of G. Todd Milne (Inventor 7) that describes additional examples similar to those in the specification has been considered. However these examples (as shown in the declaration) still do not describe what metabolic pathways are modulated. The examples (both in the declaration and instant specification) appear to comprise transfection of a cell with a modified gene (and/or a homolog of said gene) and assessing the results. Are these modified genes (and/or a homologs of said genes) part of a regulatory pathway of secondary metabolite production or not? Are these homologs all functioning in a similar manner or can they be assumed to function similarly in all fungal species? Many pathways and genes can be affected by the transfection of the modified gene and/or homolog. The examples appear to simplify a complex and tightly regulated process of secondary metabolite production. Also one cannot be certain that these experiments will improve secondary metabolite production in any fungal species as the host cells used in the examples are predominantly *Aspergillus terreus* and *Penicillium chrysogenum*. The instant specification discloses an example wherein the cAMP-dependent protein kinase TPK2 from *Saccharomyces cerevisiae* is overexpressed in *Aspergillus terreus* to improve the production of lovastatin and the declaration shows in example 6 the transformation of *Aspergillus terreus* with a lov E gene to improve the production of lovastatin. Both of these genes (TPK2 and lov E) are excluded from the instant invention as claimed thus it is unclear how these examples can be related to the instant invention as claimed. Example 7 of the declaration exemplifies the aspect of the claimed invention wherein the modulation of a gene involved in the regulation of secondary

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metabolite production is mediated by a small molecule. Cycloheximide and lovastatin were incubated with *Monascus* host cells to test the production of red pigment in the cells. What gene (and/or pathway) is being modulated in this experiment? Cycloheximide is a protein synthesis inhibitor and thus would affect many cellular pathways and not solely affect the pathways that regulate secondary metabolite production. It is unclear how this example relates to the instant invention as claimed. One of skill in the art would need to rely on "trial and error" experimentation in order to first discern the metabolic pathways and their regulation before one can successfully genetically manipulate the pathways to increase the production of a secondary metabolite. Thus the claimed invention is still considered to be unpredictable.

Applicants' assert that the uncertainty of genetic engineering in fungi is not as substantial as suggested by the Office Action mailed May 22, 2001 and provided references to support this assertion. However, two of these references (Chang *et al.* and Kennedy *et al.*) discuss the modulation of biosynthetic genes. The instant invention is drawn to modulation of the expression of genes involved in the regulation of secondary metabolite production and not modulation of the biosynthetic genes themselves. The last two references (Theilgaard *et al.* and Tag *et al.*) were published after Applicants' priority date and thus were unavailable as art at the time of invention. References published after the priority date of an application are not sufficient to establish the state of the art in a field at the time of invention.

Furthermore, the art indicates that in 2000 (a year after the applicants' priority date) improving the biosynthesis of a secondary metabolite is still considered to be complex and thus uncertain (see Parekh *et al.* Applied Microbiology and Biotechnology 54(3):287-301 2000). According to Parekh *et al.* over-production of secondary metabolites requires expertise in many

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areas including physiology, pathway regulation and fermentation processes for each type of organism (see abstract). Parekh *et al.* states that ... "the assembly of a complex secondary metabolite is connected with widely unknown specific reactions involving different biosynthetic enzymes..." and further "...rate-limiting enzymatic reactions or flux nodes are unknown in most if not all pathways and probably change with each new culture." Thus, Parekh *et al.* concludes "...with only limited knowledge of the physiology and genetics associated with the production of each molecule of interest, one is often led to an empirical approach to strain improvement." (see page 288, left column for above series of quotations). An empirical approach constitutes undue "trial and error" experimentation.

The instant invention as claimed in claims 1-28, 102 and 103 is not enabled for improving the production of a secondary metabolite in a fungus. Therefore, for both the reasons above and the reasons made of record in the previous Office Action mailed on May 22, 2001, the rejection of claims 1-28, 102 and 103 under 35 U.S.C 112, first paragraph is maintained.

Conclusion

Claims 1-28, 102 and 103 are rejected. Claims 1-28, 102 and 103 are free of the prior art. The closest prior art with regard to claims 1-28, 102 and 103 is WO 99/25865 (IDS reference). WO 99/25865 discloses similar methods for genetic manipulation of fungal genes however does not contemplate the modulation of the same genes considered for modulation in the instant invention.

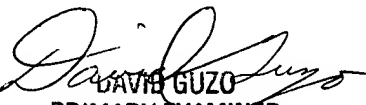
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katharine F. Davis whose telephone number is (703) 605-1195 with direct desktop RightFax (703) 746-5199. The examiner can normally be reached on Monday-Friday (8:30am-5:00pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications. Any inquiry of a general nature or any inquiry concerning the formalities of this application should be directed to Patent Analyst Tracey Johnson whose telephone number is (703) 305-2982.

Katharine F. Davis
March 4, 2002


DAVID GUZO
PRIMARY EXAMINER